UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,259	07/21/2004	Patrick, Arnoldus, Maria Van Buggenum	0-2002.712 US	9811

67706 7590 12/29/2008

ORGANON USA, INC.
c/o Schering-Plough Corporation
2000 Galloping Hill Road
Mail Stop: K-6-1, 1990
Kenilworth, NJ 07033

EXAMINER	
BADIO, BARBARA P	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jill.corcoran@spcorp.com
patents@spcorp.com
nancy.joyce.simmons@spcorp.com

Office Action Summary	Application No.	Applicant(s)	
	10/502,259	VAN BUGGENUM ET AL.	
	Examiner	Art Unit	
	Barbara P. Badio	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Nonfinal Office Action on the Merits

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

2. The use of the trademark "LIVIAL" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 103

3. The rejection of claims 1-9 under 35 USC 103(a) over Babcock et al. (US 3,341,557), Campbell et al. (Steroids, 1963) and Loozen et al. (WO 01/05806) is withdrawn.

4. Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Babcock et al. (US 3,341,557) and Campbell et al. (Steroids, 1963).

Each of Babcock and Campbell teaches the production of 7α-methyl derivatives of steroid compounds by reacting the corresponding 4,6-diene-3-ketone compounds with a methyl Grignard reagent, such as methyl magnesium iodide and methyl

magnesium bromide, in the presence of a cuprous salt such as cuprous chloride (see each in its entirety, especially see **Babcock**, col. 6, line 71 - col. 7, line 19 and Examples 1,3, 5, 27 etc.; **Campbell**, paragraph bridging pages 317-318 and Scheme on page 319). Campbell teaches selectivity and good yield of the 7α- derivatives when Grignard reagent is utilized in the presence of a cuprous salt in the instant process (see page 318, lines 1-4). Babcock teaches solvents such as tetrahydrofuran and ether (see col. 7, lines 4-7); temperature of -40°C to the boiling point of the reaction mixture (see col. 7, lines 7-11) and the use of at least five moles of Grignard per mole of steroid (see col. 7, lines 15-17).

The instant claims differ by the recitation of a trialkylsilyl protected starting material in the process taught by each of Babcock and Campbell. However, acyl groups such as acetyl and trialkylsilyl groups such as trimethylsilyl are well known hydroxyl protecting groups (see for example **US 4,400,393**, col. 1, lines 31-40). Based on the level of skill of the ordinary artisan in the chemical art and the knowledge of hydroxyl protecting group, it would have been obvious to the skilled artisan in the art at the time of the present invention to utilize other well known hydroxyl protecting groups, including trialkylsilyl groups, in the process taught by Babcock and Campbell with the reasonable expectation that the reaction would run to completion with the production of the desired 7α-methyl substituted steroid compound.

It should be noted that the use of analogous reactants in a known process is prima facie obvious. *In re Durden*, 226 USPQ 359 (1985). Once the general reaction has been shown to be old, the burden is on Applicants to present reasons or authority

for believing that a group on the starting material would take part in or affect the basic reaction and, thus, alter the nature of the product or the operability of the process. In looking at the instant claimed process as a whole, as stated in *In re Ochiai*, 37 USPQ2d 1127 (1995), the claimed process would have been suggested to one skilled in the art.

Claim 3 further differs by reciting CH_3MgCl. However, CH_3MgCl is a well known Grignard reagent (see for example, US 4,298,559, col. 4, lines 8-19; US 7,304,157, col. 13, lines 63-65).

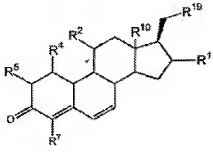
Claim 6 further differs by reciting specific concentrations of steroid of formula (11). However, the court has held that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Russell*, 439 F.2d 1228, 169 USPQ 426 (CCPA 1971).

5. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Babcock et al. (US 3,341,557) and Campbell et al. (Steroids, 1963) as applied to claim 1-9 above, and further in view of Peters et al. (WO 01/58919).

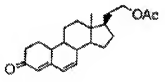
Babcock and Campbell are discussed above in #4. The instant claim differ by reciting 21-hydroxyl-19-norpregn-4,6-dien-3-one.

However, Peter teaches a genus of 4,6-diene steroid derivatives of the formula

(XXVIII)



wherein R^{19} is hydroxylmethyl or a protected hydroxylmethyl group (see page 26 and claim 8 for definition of R^{19}). Peter exemplifies



in the production of the corresponding 7α-methyl derivative (see Figure 8, compound 9). Based on the level of the skill of the ordinary artisan in the art, it would have been obvious to make the acetate derivative exemplified by Peters utilizing the corresponding free 21-hydroxy derivative taught therein. It would also have been obvious to the skilled artisan in the art to modify the process of Babcock and Campbell utilizing any 21-hydroxyl protected derivative of the compound of Peters therein, including that of compound 9 of Peters, with the reasonable expectation of obtaining the corresponding 7α-methyl derivative.

Again, it is noted that the use of analogous reactants in a known process is prima facie obvious. *In re Durden*, 226 USPQ 359 (1985). Once the general reaction has been shown to be old, the burden is on Applicants to present reasons or authority for believing that a group on the starting material would take part in or affect the basic

reaction and, thus, alter the nature of the product or the operability of the process. In looking at the instant claimed process as a whole, as stated in *In re Ochiai*, 37 USPQ2d 1127 (1995), the claimed process would have been suggested to one skilled in the art.

6. The rejection of claim 10 under 35 USC 1039a) over Peters et al. (WO 01/58919) is maintained.

Applicant argues the difference in the 7α-alkylation processes of Peters versus the instant invention. According to applicant, based on the difference, there is no motivation to modify the compound exemplified by Peters to obtain the claimed compound of a free alcohol intermediate used to prepare the trialkylsilyl protected substrate of the current application. Applicant's argument was considered but not persuasive for the following reasons.

First, the issue is not the difference(s) between the process of Peters and that of the claimed invention, but whether the claimed compound is obvious in view of the teachings of Peters. As stated in the previous Office Action, the genus of 4,6-dienes of formula XXVIII taught by Peters is inclusive of both the free 21-hydroxyl and protected hydroxyl groups. Thus, the claimed compound is obvious since a reference is not limited to its working examples but is evaluated for what it teaches those of ordinary skill in the art.

Secondly, if one agrees that the acetyl group is needed in the process of Peters, said teaching does not make the free hydroxyl derivative unobvious. The fact is, it would have been well within the level of skill of the ordinary artisan in the art to make

compound 9 exemplified by Peters from the corresponding free alcohol taught by the reference. Thus, said alcohol would be prima facie obvious.

For these reasons and those given in previous Office Action, the rejection of claim 10 under 35 USC 1039a) over Peters et al. (WO 01/58919) is maintained.

Response to Arguments

7. Applicant's argument against Babcock and Campbell is noted. Briefly, applicant argues the prior art process would result in mixture of 7α- and 7β-methyl compounds whereas the claimed process markedly improved the stereoselectivity of the Grignard reaction in favor of the desired 7α-methyl isomer. Applicant's argument was considered but not persuasive for the following reason.

Applicant's argument centers on the difference in the hydroxyl protecting groups. It should be noted that the process taught by the prior art as discussed on page 2 of the present specification is inclusive of the general process of the claimed invention and that of Babcock and Campbell, i.e.,

> cuprous chloride or cupric acetate catalyzed 1,6-conjugate addition of alkylmagnesiumhalogens to 4,6-unsaturated 3-ketosteroids.

Thus, the only difference between the prior art process and the instantly claimed process is the hydroxyl protecting group.

Campbell teaches selectivity and good yield of the 7α-methyl isomer when Grignard reagent is utilized in the presence of a cuprous salt (see page 318, lines 1-4 of Campbell). Therefore, applicant's argument that the prior art process would not result in stereoselectivity is noted but not persuasive.

If applicant wants to argue unexpected/unobvious results utilizing a trialkylsilyl protecting group versa the acetate group exemplified by the prior art, a true side-by-side comparison would be necessary. Applicant has not provided said comparison because said comparison would keep the process, including the reaction conditions and reactants, constant with the only difference being in the hydroxyl protecting group of the starting material. It should be noted that said comparison might not be unexpected and/or unobvious if the skilled artisan in the art would expect differences in the yield of a compound based on variation of the protecting group.

The reference to US 5,342,834 is noted but can not take the place of a true side-by-side comparison because the skilled artisan would be aware that differences in the reaction condition(s) can affect the outcome of a process.

Telephone Inquiry

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Barbara P. Badio whose telephone number is 571-272-0609. The examiner can normally be reached on M-F from 6:30am-4:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Barbara P. Badio/
Primary Examiner, Art Unit 1612